

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.
Petitioner

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2025-01194
Patent No. 9,051,542

PATENT OWNER'S PRELIMINARY RESPONSE

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Exhibit No.	Description
2001	Declaration of Katherine A. Helm
2002	Complaint, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 1 (1:24-cv-00882-UNA)
2003	Second Amended Complaint, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81, (1:24-cv-00882-UNA)
2004	Second Amended Complaint, Ex. K, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81-2 (1:24-cv-00882-UNA)
2005	Second Amended Complaint, Ex. M, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81-3 (1:24-cv-00882-UNA)
2006	<i>Collabo Innovations, Inc. v. Sony Corp.</i> , 15-cv-1094-RGA, D.I. 43 (D. Del. Jan. 5, 2017)
2007	<i>Ansell Healthcare Prods. LLC v. Reckitt Benckiser LLC</i> , 15-cv-915-RGA, D.I. 105 (D. Del. Dec. 1, 2016)
2008	<i>RainDance Techs., Inc. v. 10X Genomics, Inc.</i> , 15-cv-152-RGA, D.I. 27, 37 (D. Del. Feb. 29, 2016)
2009	Notice of Service of Plaintiff's Initial Claim Chart, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 59 (1:24-cv-00882-UNA)
2010	Notice of Service of Stipulation to Extend Time, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 68 (1:24-cv-00882-UNA)
2011	So Ordered re 77 Joint Stipulation to Amend Scheduling Order, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 78 (1:24-cv-00882-UNA)
2012	Notices of Service for Interrogatories and Requests for Production, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 28 (1:24-cv-00882-UNA)

Exhibit No.	Description
2013	A.R. Kucernak et al., <i>Avoid Using Phosphate Buffered Saline (PBS) as an Electrolyte for Accurate OER Studies</i> , 9 ACS Energy Lett. 3939–3946 (2024)
2014	Oral Order on April 5, 2016 Denying Motion to Stay, <i>RainDance Technologies, Inc. et al v. 10X Genomics, Inc.</i> (1-15-cv-00152)
2015	A.E. Smith, “ <i>Gene Therapy: Where Are We</i> ,” 354 The Lancet SI1 (July 1999)
2016	<i>Remington: The Science and Practice of Pharmacy</i> , Nineteenth Ed., Vol. I, Chapters 17, 18, 23, and 36 (1995).
2017	<i>Remington: The Science and Practice of Pharmacy</i> , Nineteenth Ed., Vol. II, Chapter 87(1995).
2018	Carpenter, J. F. & Manning, M.C. (Eds.), <i>Rational Design of Stable Protein Formulations: Theory and Practice</i> , Vol. 13 (2002).
2019	Gatlin, L., Chapter 17, “Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parental Products,” in <i>Injectable Drug Development: Techniques to Reduce Pain and Irritation</i> , (eds. P. Gupta and G. Brazeau), pp. 401-421 (1999).
2020	International Patent Pub. No. WO 99/41416 to Frei, et al.
2021	Croyle, et al., “Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy,” <i>Gene Ther.</i> , 8:1281-1290 (2001).
2022	Adadevoh, K. et al., “A Short-Term Field Use and Shipping Stability Study of a Wild Type Ad5 Adenoviral Reference Material,” <i>BioProcessing</i> 1(2) 62-69 (2002).
2023	Declaration of Martin Christopher Davies in Support of Patent Owner’s Preliminary Response (“Davies”)
2024	Curriculum Vitae of Martin Christopher Davies
2025	Ayache, J. et al., <i>Sample Preparation Handbook for Transmission Electron Microscopy</i> . (2010).
2026	Arista-Romero, M. et al., “Towards a Quantitative Single Particle Characterization by Super Resolution Microscopy: From Virus

Exhibit No.	Description
	Structures to Antivirals Design.” (2021).
2027	Chu, J. et al., “A bright cyan-excitable orange fluorescent protein facilitates dual-emission microscopy and enhances bioluminescence imaging in vivo.” <i>Nat Biotechnol.</i> 2016 July ; 34(7): 760–767 (2016).
2028	Aaron, K. et al., “Selection of Viral capsids and promoters affects the efficacy of rescue of Tmprss3-deficient cochlea.” <i>Molecular Therapy: Methods & Clinical Development</i> (2023).
2029	Jia, F. et al., “A nonviral minicircle vector for deriving human iPS cells” <i>Nature Methods</i> (2010).
2030	[Reserved]
2031	J.O. Konz et al. “Development of a Purification Process for Adenovirus: Controlling Virus Aggregation to Improve the Clearance of Host Cell DNA,” 21 <i>Biotechnol. Prog.</i> 466 (2005)
2032	Booy, F. P., et al. “Electron microscopy of influenza virus: a comparison of negatively stained and ice-embedded particles.” <i>Journal of Molecular Biology</i> 184.4 (1985): 667-676.

Patent owner Genzyme Corp. (“Genzyme” or “Patent Owner”) respectfully submits this preliminary response to the *Inter Partes* Review (“IPR”) petition filed by petitioner, Sarepta Therapeutics, Inc. (“Sarepta”), alleging that claims 3-6 (the “challenged claims”) of U.S. Patent No. 9,051,542 (EX1001, the “’542 patent”) are obvious (the “Petition”).

I. INTRODUCTION

This is the third IPR to challenge validity of the ’542 patent. The two prior IPR challenges were denied institution on the merits (*infra* §III). So too here, Sarepta’s Petition fails to establish any reasonable likelihood that at least one of the challenged claims is unpatentable. Sarepta’s Petition fails to provide any new art or arguments that would compel the Board to deviate from its thorough and well-reasoned institution denials in the prior IPRs, particularly where doing so would upend settled expectations surrounding a patent that issued more than 10 years ago and has already expired.¹

¹ Genzyme reserves its right to oppose the IPR of the ’542 patent based on a holding that the Board lacks the authority to review the patentability of expired patent claims. See Petition for Writ of Certiorari, *Gesture Tech. Partners, LLC v. Apple Inc.*, No. 24-1280 (June 16, 2025).

The '542 patent claims an inventive breakthrough in recombinant adeno-associated virus ("rAAV") compositions for use in gene therapy, developed over twenty years ago by inventors at Avigen Inc and acquired by Genzyme. Administering rAAV vectors to patients "may require small volumes of highly concentrated vector." EX1001, 2:12-13. The development of storable concentrated rAAV compositions was hindered by rAAV particle aggregation, which caused loss of infectivity, biodistribution issues, and adverse immune responses. *Id.*, 2:15-39. Without solving the problem of rAAV aggregation, gene therapy formulations would be therapeutically ineffective. EX2015, 4 ("[H]igh doses of viral vector ... are usually required to achieve measurable gene transfer"); EX1047, 1; EX1043, 1.

While this problem and its severity were well-documented in the prior art, the '542 patent inventors were the first to solve it. They surprisingly formulated rAAV compositions that could be stored without significant aggregation by increasing the ionic strength to greater than 200 mM. Ex. 1001, 7:1-22.

When seeking approval of its own gene therapy product, Elevidys[®], Sarepta cited the '542 patent inventors' discovery—that high ionic strength minimized rAAV aggregation—as being critical to the development of Elevidys[®]. *Infra* §II.C. Now, years later, Sarepta belies its contemporaneous statements by arguing the '542 patent's claims are obvious. Sarepta cobbles together piecemeal art for each claim element, including the claimed rAAV concentration and ionic strength

limitations. Establishing obviousness, however, requires the evaluation of the claimed combination as a whole to guard against “hindsight reasoning, using the invention as a roadmap to find its prior art components.” *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Yet, improper hindsight and speculation by Sarepta’s expert, Dr. Mark A. Kay (EX1005, the “Kay Declaration”), is all that props up its Petition. The Petition fails to establish that a person of ordinary skill in the art (“POSA”) would have been motivated to make a concentrated rAAV composition having high ionic strength. It also fails to establish a POSA would have reasonably expected that high ionic strength compositions would not exhibit significant aggregation.

Sarepta also disregards teachings that contradict its arguments. It is a “longstanding principle that the prior art must be considered for all its teachings, not selectively” for only those teachings that allegedly support obviousness. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Konz (EX1008), which Sarepta relies on in all grounds for the ionic strength element (Petition, 35-37, 53-55), never discloses a “formulation buffer” with close to an ionic strength of 200 mM. Konz directs a POSA to lower, not higher, ionic strength rAAV compositions. Sarepta also cites Evans (EX1020), which Konz “incorporates [] by reference.” Petition 35-36, 53-54. But Evans is the same

reference relied on in a prior failed IPR challenging the '542 patent. *Infra* §III.B.

Evans never connects high ionic strength with improved adenoviral composition properties. The Board expressly found Evans unpersuasive for proving the challenged claims obvious, including the ionic strength element. EX1017, 23-24.

Sarepta's Petition and the Kay Declaration also fail to support its additional "Hail Mary" arguments. Neither Wu nor Potter discloses high-concentration rAAV compositions with high ionic strength. Petition, 35, 53. Sarepta ignores other prior art indicating that high salt concentration therapeutic compositions, like the ones Sarepta relies on for disclosures relating to ionic strength, were associated with tissue damage and pain when injected. Neither does Sarepta address prior art demonstrating that high salt concentration compositions led to rAAV instability. Finally, Sarepta's citation of far afield, 1970s publications relating to polio virus aggregation in wastewater is irrelevant to therapeutic rAAV compositions. *Id.*, 11, 19 (citing EX1030, EX1031, EX1032). Such literature would not motivate a POSA to make high ionic strength rAAV compositions. For all these reasons, Sarepta fails to establish a reasonable likelihood of succeeding in this Petition. As with the prior '542 patent IPR petitions, the Board should deny institution.

II. THE '542 PATENT

The '542 patent issued on June 9, 2015, claiming priority to a nonprovisional application filed in 2005 and two provisional applications filed in

2004. The specification describes how the inventors overcame the challenge of concentration-induced rAAV aggregation. Their invention also ensured the resulting rAAV compositions would be suitable for human parenteral administration (EX1001, 5:10-20), including considerations of tonicity, pH, and the pharmaceutical acceptability of excipients. The balancing of these considerations elevated the complexity of solving the rAAV aggregation problem.

A. Disclosed Invention

After many unsuccessful attempts at developing storable rAAV compositions, the inventors discovered that high ionic strength was the key to preventing vector aggregation in compositions suitable for human administration. *Id.*, Abstract. The inventors studied vector aggregation in solutions of sodium chloride, sodium citrate, sodium phosphate, sodium sulfate, magnesium sulfate, and glycerol and tracked aggregation as a function of two parameters, osmolarity (Figure 1A) and ionic strength (Figure 1B). *Id.*, 6:63-65, 12:33-67 (Example 3), FIGS. 1A, 1B.

Osmolarity measures the number of particles of solute per liter. For a salt that fully dissociates, like NaCl, there are two solute particles, one Na⁺ and one Cl⁻, for every equivalent of NaCl. EX2023 (“Davies”), ¶¶31-34 (citing EX2016, 56). Therefore, the osmolarity of NaCl, expressed in osmols, is double its molarity. *Id.*, ¶34. For magnesium chloride (MgCl₂), which contains three particles of solute, one

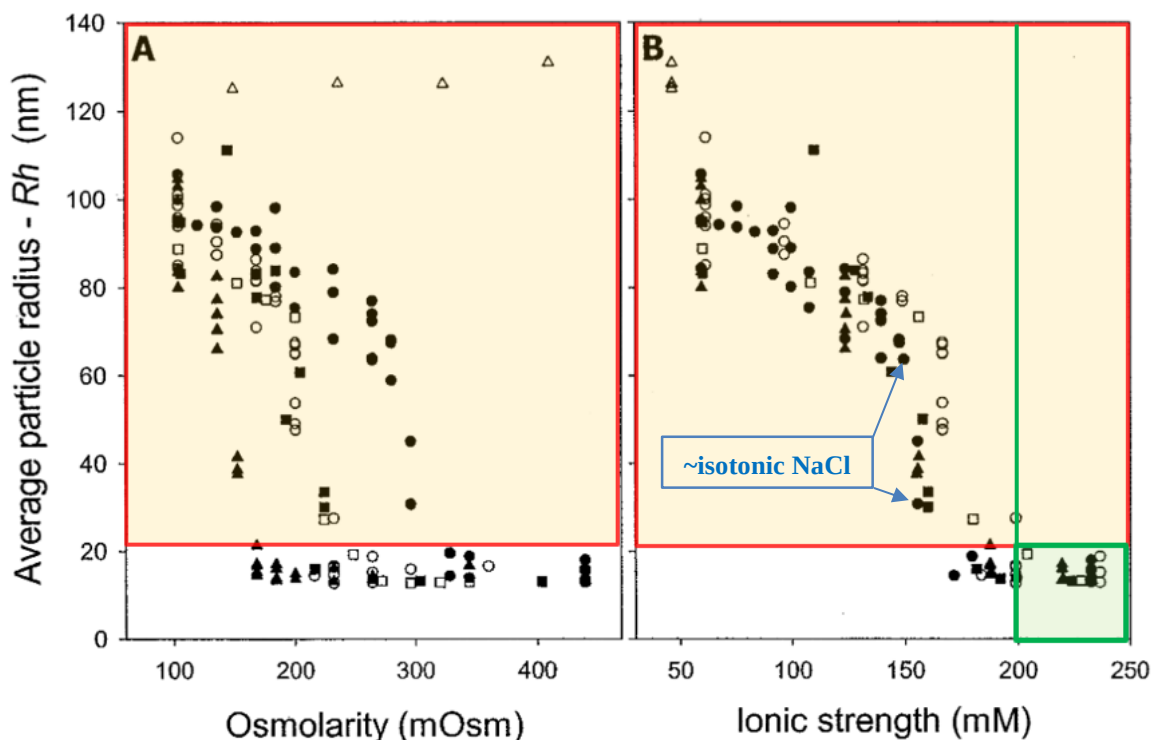
Mg²⁺ and two Cl⁻ ions, the osmolarity is triple the molarity of MgCl₂. *Id.*, ¶35. A concept related to osmolarity is tonicity. A therapeutic composition is isotonic with human serum if it has the same osmolarity as human serum, hypertonic if greater than, or hypotonic if less than. *Id.*, ¶¶36-37. When administered, hypertonic and hypotonic compositions can cause pain and tissue damage, so formulators seek to make isotonic compositions. *Id.*, ¶¶38-40.

“Ionic strength is a measure of the intensity of the electrical field in a solution” and it increases exponentially as a function of an ion’s charge. *Id.*, ¶41. (citing EX2016, 5). A 100 mM NaCl solution has an osmolarity of 200 mOsm and an ionic strength of 100 mM, whereas a 100 mM MgCl₂ solution has an osmolarity of 300 mOsm and an ionic strength of 300 mM. *Id.*, ¶42. This illustrates that the ionic strength of multivalent ion-containing salts (*e.g.*, MgCl₂) is higher per osmol than salts of monovalent ions (*e.g.*, NaCl). *Id.*, ¶¶43-45.

Figures 1A and 1B present data showing aggregation of AAV vector particles as a function of osmolarity and ionic strength, respectively. EX1001, 4:14-16. In Figures 1A and 1B, “[a]verage particle radius is measured by dynamic light scattering (DLS) following vector dilution in varying concentrations of excipients buffered with 10 mM sodium phosphate at pH 7.5.” *Id.*, 4:18-21; Davies, ¶¶49-51. The average radius of rAAV particles is approximately 13 nm so

“Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation.” *Id.*, 9:26-27; Davies, ¶¶63-64.

In annotated Figures 1A and 1B below, the excipients are denoted as follows: sodium chloride (NaCl) (●), sodium citrate (Na₃(C₆H₅O₇)) (○), sodium phosphate (Na₃(PO₄)) (▪), sodium sulfate (Na₂(SO₄)) (□), magnesium sulfate (Mg(SO₄)) (▲), and glycerol (C₃H₈O₃) (Δ):



Id., FIGS. 1A, 1B (annotation added). In both Figures, compositions falling within the orange shaded portion of the plots exhibited significant aggregation (Rh > 20 nm), whereas compositions in the unshaded or green shaded portions of the plot did not (Rh < 20 nm).

The results of Figure 1A, which plots particle radius as a function of osmolarity, showed no consistent relationship between aggregation and osmolarity across the tested excipients. At the extremes, “magnesium sulfate [(▲)] prevent[ed] aggregation at >200 mOsm whereas sodium chloride [(●)] require[d] ≥ 350 mOsm to achieve a similar effect,” while glycerol (Δ) never prevented aggregation even at >400 mOsm. *Id.*, FIG. 1A, 7:1-8; Davies, ¶65.

Figure 1B shows data from the same experiment “plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient.” EX1001, 7:18-20. In contrast to Figure 1A’s particle radius versus osmolarity plot, Figure 1B’s plot of particle radius versus ionic strength shows a clear trend; “vector aggregation is prevented when **ionic strength is ~200 mM or greater** regardless of which salt is used” as shown by the green line at 200 mM ionic strength in annotated Figure 1B, above. *Id.*, 7:20-22.² These data led to the breakthrough “that the ionic strength (μ) of a solution ... is the **primary factor affecting aggregation.**” *Id.*, 7:22-25. The green box in annotated Figure 1B illustrates the scope of claim 5 requiring both an “ionic strength ... greater than 200 mM” and “an average particle radius (R_h) of less than about 20 nm as measured by dynamic light scattering.” *Id.*, 14:23-24, 14:35-37; ; Davies, ¶66.

² Emphasis is added unless otherwise noted.

The identification of ionic strength as a key to preventing aggregation unlocked a new path. Isotonic compositions for human parenteral administration that did not exhibit significant aggregation could be made by employing multivalent ions to adjust ionic strength. As the inventors explained, “[o]f practical concern, commonly used buffered saline solutions have insufficient ionic strength to prevent AAV2 vector aggregation at concentrations exceeding 10^{13} particles/mL.” EX1001, 4:65-67. “[I]sotonic (150 mM) [NaCl] has an ionic strength of 150 mM, a value insufficient to maintain AAV2 solubility at high vector concentrations,” as shown in annotated Figure 1B. *Id.*, 5:15-17. Thus, making a concentrated rAAV composition in NaCl would require the formulation to be hypertonic. *Id.*, 5:4-7; Davies, ¶67.

Because of the exponential relationship between ionic strength and charge valency, “multivalent ions” (*i.e.*, ions having a charge of two or more) “achieve a similar degree of inhibition of aggregation at lower concentrations than monovalent [NaCl],” for which Na^+ and Cl^- only contribute one charge each. EX1001, 7:1-8. Davies, ¶¶68, *see also id.*, 42-46. The inventors recognized and capitalized on the “exponential relationship of ionic strength with charge valency ... to develop isotonic formulations with high ionic strengths.” EX1001, 5:7-10. Compositions containing multivalent ions, including pharmaceutically acceptable excipients containing citrate, sulfate, magnesium, and/or phosphate can be

formulated with an ionic strength of greater than 200 mM while remaining isotonic because multivalent ions have high ionic strength even at low concentrations.

The inventors analyzed data from particle size detection (*id.*, 9:5-50 (Table 3)) and percent product recovery following filtration (*id.*, 7:65-8:40 (Table 2)), to confirm that high ionic strength compositions did not exhibit significant rAAV aggregation. Davies, ¶¶52-53. The inventors prepared three solutions for AAV2-AADC vectors: “Control Formulation (CF: 140 mM sodium chloride, 10 mM sodium phosphate, 5% sorbitol, pH 7.3); Test Formulation 1 (TF1: 150 mM sodium phosphate, pH 7.5); and Test Formulation 2 (TF2: 100 mM sodium citrate, 10 mM Tris, pH 8.0).” *Id.*, 11:66-12:3. In Experiment 1 the samples contained 2.5×10^{13} vg/ml vector, and in Experiment 2 the samples contained 6.7×10^{13} vg/ml vector. *Id.*, 12:4-11; Davies, ¶¶69.

In Example 2, the exemplary formulations were filtered through a 0.22 μ m filter. EX1001, 8:1-9, 11:52-12:29. Table 2 summarizes the results of Experiments 1 and 2, including the ionic strength of each formulation. *Id.*, 8:19-44.

TABLE 2

AAV VECTOR RECOVERY AT PROCESS SCALE					
Experiment	Formulation	μ (mM)	Target (vg/mL)	Actual (vg/mL)	Yield % (RSD)
1	CF	160	2.5E13	1.93E13	77 (6.6)
1	TF1	310	2.5E13	2.38E13	95 (7.4)
1	TF2	510	2.5E13	2.33E13	93 (7.4)
2	CF	160	6.7E13	3.98E13	59 (6.0)
2	TF2	510	6.7E13	6.42E13	96 (4.4)

As Table 2 shows, recoveries exceeded 90% following filtration in formulations TF1 and TF2 having ionic strengths greater than 200 mM, whereas recovery from CF formulations, having ionic strength of 160 mM, was only 77% and 59% for experiments 1 and 2, respectively. Davies, ¶¶70-71.

The inventors also conducted storage and freeze-thaw (“F/T”) cycle studies on the CF, TF1, and TF2 formulations, with the results presented in Table 3, in which particle radius was measured by DLS to determine the presence of aggregates. EX1001, 9:5-65; Davies, ¶72.

TABLE 3								
STABILITY OF AAV2 VECTORS								
Formu- lation	Particle radius - Rh (nm)							
	4° C.		-20° C.			-80° C.		
	Pre	5 d	1 F/T	5 F/T	10 F/T	1 F/T	5 F/T	10 F/T
CF	14.5	27.0	22.4	56.1	94.5	20.6	57.5	141
TF1	13.8	16.3	TH	TH	TH	TH	TH	TH
TF2	13.8	14.4	14.2	14.0	14.1	13.8	21.3	50.9

Pre: DLS radius measured immediately following 0.2 µm filtration.

Vector concentrations (vg/mL): CF: 1.93E13, TF1: 2.38E13, TF2: 2.33E13.

TH: signal intensity is too high to measure because of extensive aggregation.

“As shown in Table 3 ... CF shows some aggregation after 5 days For vector prepared in TF1, no aggregation occurs after 5 days [of storage] at 4° C For vector prepared in TF2, no aggregation is observed at 4° C, or following up to 10 F/T cycles at -20° C” EX1001, 9:44-55. These studies further confirmed the

importance of increased ionic strength in preventing aggregation. *Id.*, 10:29-43; Davies, ¶73.

B. Challenged Claims

By virtue of their dependence from claim 1, claims 3-6 recite, *inter alia*:

- “purified, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;”
- “the ionic strength of the composition is greater than 200 mM;” and
- “the purified AAV vector particles are stored in the composition without significant aggregation.”

C. Sarepta Acknowledged the Importance of the Claimed High Ionic Strength rAAV Compositions in its Regulatory Submissions

In regulatory documentation relating to the development of its proprietary gene therapy product, Elevidys[®], Sarepta acknowledged the importance of the inventors’ discovery that high ionic strength is critical to preventing rAAV aggregation. The Biological License Application (“BLA”) for Elevidys[®] cites a publication co-authored by the inventors of the ’542 patent, John Fraser Wright, and Guang Qu, describing the importance of high ionic strength for preventing rAAV aggregation. EX2005 (citing EX1047, “Wright (2005)”). Sarepta’s BLA states that the “extent of AAV aggregation is a critical concern for safety and efficacy in a drug product. It has been reported in the literature that ionic strength is critical for the minimization of AAV aggregation (Wright 2005).” *Id.*

Wright (2005) describes the inventors' discovery that "an ionic strength of ≥ 200 mM was required to prevent aggregation" for high-concentration rAAV particle compositions. EX1047, 6. The Wright (2005) disclosure substantially overlaps with the '542 patent's disclosure. *Compare* EX1001, Figs. 1-3, Tables 1-3 *with* EX1047, Figs. 1-2, Tables 1-3. Thus, by Sarepta's own account, the claimed high ionic strength compositions are critical to the safety and efficacy of Elevidys[®].

D. Claim Construction

For this Preliminary Response only, Genzyme does not challenge the Petition's alleged constructions. Petition, 29-32.

III. THE PRIOR FAILED IPR CHALLENGES TO THE '542 PATENT

Two prior IPR petitions challenging the '542 patent were denied institution on the merits in detailed decisions. *Novartis Gene Therapies, Inc. v. Genzyme Corp.*, IPR2023-00608, Paper 20 (PTAB Aug. 30, 2023) (EX1017); *Novartis Gene Therapies, Inc. v. Genzyme Corp.*, IPR2023-00609, Paper 22 (PTAB Aug. 30, 2023) (EX1018).

A. The Board Found that the Prior Petitions Failed to Establish that a POSA Would Have Been Motivated to Make the Claimed rAAV Compositions at High Ionic Strength

Both prior institution denials found that the petitions and cited art failed to establish that a POSA would have been motivated to make rAAV compositions with an ionic strength of greater than 200 mM. EX1017, 23-24; EX1018, 27 n.10.

The Board found that although the prior art disclosed ranges of ionic strengths that, in some cases, overlapped with the claims, it was not known that ionic strength was a “result-effective variable” for rAAV aggregation. *Id.* The Board further found that petitioner, Novartis, could not show a likelihood of obviousness where it “fail[ed] to establish a known relationship between ionic strength and viral particle aggregation.” *Id.*

In IPR2025-00608, the Board found that Novartis’ citation of Evans (EX1020) specifically failed to establish a POSA’s motivation to make high ionic strength rAAV compositions. EX1017, 23-24. Notably, Sarepta relies heavily on Evans, as incorporated by Konz, for the motivation arguments in its Petition. *Infra* §§IV.B.3(b)(ii), VIII.A. Novartis’ ionic strength argument relied on disclosure from Evans’ claim 5 composition contain[ing] “‘sodium chloride from about 25 mM to about 250 mM’ and either MgCl₂ or CaCl₂ ‘in an amount from about 0.1 mM to about 5 mM.’” EX1014, 42 (citing EX1020, claim 5). Novartis argued that “[a]ccepting the high end of both ranges, Evans’ claim 5 composition comprising 250mM of NaCl and 5mM of MgCl₂ has an ionic strength of 265mM.” *Id.* Novartis argued that a “POSA would have been motivated to select the high end of the concentration ranges for NaCl and MgCl₂ in Evans’ claim 5 composition,” because “selection of an appropriate ionic strength for a therapeutic composition is a matter of routine optimization.” *Id.*, 43.

The Board rejected Novartis’s arguments. The Board explained that “data presented in Evans does not establish any clear relationship between ionic strength and maintained infectivity after storage” such that a POSA would have reason to adjust ionic strength. EX1017, 23 (citing EX1016, 22-27). The Board also found that Novartis had failed “to establish a known relationship between ionic strength and viral particle aggregation. Rather, the evidence of record teaches that ‘the mechanism of vector aggregation is not well understood, and purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration.’” EX1017 (citing EX1045, 2; EX1016, 21; EX1060, ¶¶84-85). Because the prior art and argument did not demonstrate recognition of any connection between ionic strength and aggregation, it did not provide a reason for a POSA to arrive at the claimed ionic strength. The Board concluded that the prior petitions did not establish a reasonable likelihood that the challenged claims were unpatentable.

B. Sarepta’s Petition Relies Heavily on the Same Art and Arguments Found Unpersuasive by the Board

Sarepta’s Petition falls squarely within the category of AIA challenges singled out in the USPTO’s September 16, 2025 memorandum.³ The Petition

³ C. Morgan Stewart, *PTAB Consideration of Prior Findings of Fact and Conclusions of Law* (Sept. 16, 2025).

challenges both the same claims (claims 5 and 6) and substantially similar claims (claims 3 and 4) addressed in the prior IPRs. All challenged claims depend from claim 1 and share elements, including the recited rAAV concentration range and an ionic strength greater than 200 mM that the Board previously found nonobvious.

Sarepta's Petition does not warrant a different outcome than IPR2023-00608. The Petition relies on the same citation to Evans' NaCl concentration range to satisfy the ionic strength limitation. The Board found this unpersuasive in its institution denial. Genzyme addressed this issue in its discretionary denial briefing in the context of 35 U.S.C. § 325(d). Paper 8. Genzyme raises this issue again here because Sarepta's reliance on the same art and argument is also relevant to the recent guidance requiring a "more detailed explanation" if the Board departs from its prior institution denials. There is no reason for the Board to make such a departure.

Sarepta purports to rely on Konz (EX1008) for the ionic strength element, not Evans (EX1020). The Petition's sections on the ionic strength limitation, however, cite Konz only to the extent it "incorporates Evans by reference." Petition, 35-36, 53-54 (citing EX1020). This means Sarepta relies on Konz in name only.

Despite contending its arguments are "materially different" (Petition, 18 (citing EX1017, 17-21)), the Petition's ionic strength arguments substantively rely

on the same disclosure in Evans as the petition in IPR2023-00608. The petition in IPR2023-00608 states “Evans’s claim 5 composition comprising **250 mM of NaCl and 5mM of MgCl₂ has an ionic strength of 265 mM.**” EX1014, 35 (citing Evans, claim 5); *see also id.* at 36-37 (citing Evans, 9:16-20, 11:13-19); EX1017, 14, 18-20 (discussing Evans’ sodium chloride concentration range disclosures cited in the petition (EX1014) and preliminary response (EX1016)). Sarepta’s Petition states “Evans ... discloses formulation buffers ... which include[] a multivalent ion, a non-ionic surfactant, and **NaCl at a concentration up to 250 mM** A POSA would have understood that the **ionic strength of this buffer would be at least 250 mM.**” Petition, 35-36. (citing EX1020 (Evans), 11:31-12:4, 14:15-28, 11:13-30, 36:21-22 (claim 4), 41:14-15 (claim 37)). Both the IPR2023-00608 and this Petition rely upon the same Evans disclosure of a buffer having ≥ 250 mM NaCl as being the major contributor to ionic strength.

After again relying on Evans for the ionic strength disclosure, and further repeating the failures of IPR2023-00608, neither Sarepta’s Petition nor the Kay Declaration explain *why*, out of all the buffers in Evans ranging from low (25 mM) to high (>250 mM) ionic strength, a POSA would have chosen the >250 mM ionic strength buffer. EX1005, ¶¶313-314, 415-416. Similarly, the Petition states that “Konz discloses methods that inhibited particle aggregation, including by reference to Evans.” Petition, 36 (citing EX1005, ¶318); 54 (citing EX1005, ¶420). But

neither the Petition nor Kay Declaration explain where Konz discloses any specific high ionic strength buffer system from Evans for use in its viral particle aggregation analysis. *Id.* Where Konz discloses “formulation buffers,” they contain between 10 mM and 75 mM of NaCl. EX1008, 25:20-27 (citing EX1020 (Evans), 30:15-19, 42:14-16). The 10 mM and 75 mM NaCl concentrations in Konz’s “formulation buffers” are far below the NaCl concentration of 250 mM cited by the Petition. Sarepta ignores that Konz undercuts the Petition’s alleged motivation to make rAAV compositions with a high ionic strength buffer. A POSA following Konz would have made a formulation buffer containing 10 to 75 mM NaCl, which would have an ionic strength well below the claimed 200 mM threshold. *Infra* §IV.A.1.b.i.

The Petition suffers from the same fatal flaw as IPR2023-00608: it fails to explain why a POSA would choose a high ionic strength buffer over the lower ionic strength formulation buffers favored by both Evans and Konz. The “background, state of the art references” from the 1970s that Sarepta alleges “demonstrate that a POSA at the relevant date would have been well aware that ionic strength was a ‘results-effective variable’ for viral particle aggregation” would not have been considered by a POSA. Petition, 19 (citing EX1030; EX1031; EX1032). These references relate to research on the disinfection of wastewater using toxic chemicals, including chlorine and bromine, to destroy viral infectivity.

Infra §IV.A.1.f. Sarepta fails to establish why a POSA “in the field of gene therapy, including development of viral vector formulations” for therapeutic treatment (EX1005, ¶166), would consider literature about disinfecting sewage. Sarepta fails to supply any reason for the Board to decide this Petition differently than the prior IPRs. Denial of institution is warranted.

IV. THE PETITION FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 3-6 ARE OBVIOUS

Sarepta fails to meet its burden to establish a reasonable likelihood of obviousness of an rAAV composition meeting all the limitations of the challenged claims, *i.e.*, comprising purified rAAV particles “at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml ... wherein the ionic strength of the composition is greater than 200 mM ... and wherein the purified AAV vector particles are stored in the composition without significant aggregation.” Sarepta’s arguments for all Grounds have at least four major failings.

The Petition alleges that a POSA would have been motivated to make high salt concentration rAAV compositions to achieve high ionic strength. Petition, 35-36, 53-54. The Petition fails to establish that a POSA would have had any motivation to increase the ionic strength of rAAV compositions to prevent aggregation. The cited literature does not establish any connection between rAAV aggregation and ionic strength in stored compositions.

State of the art references through 2004 undermine Sarepta's motivation argument. A POSA would have understood that high salt concentration therapeutic compositions are "hypertonic." Hypertonic compositions were known to cause tissue damage and pain upon injection. This would have led a POSA to avoid making high salt concentration therapeutic compositions.

Prior art publications also showed that high salt concentrations destabilized viral particle compositions. These studies would have further deterred a POSA from making high salt concentration rAAV compositions.

Finally, the Petition fails to establish why a POSA would have reasonably expected that the claimed high-concentration rAAV compositions could be stored without significant aggregation. Any one of these failings results in the Petition's failure to prove the challenged claims obvious.

A. Ground 1: The Petition's Combination of Wu and Konz Fails to Render Claims 3-6 Obvious

Sarepta assembles several disclosures from Wu and Konz, alleging that the combined references satisfy each claim element, including (i) "purified, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;" (ii) "wherein the ionic strength of the composition is greater than 200 mM;" and (iii) "wherein the purified AAV vector particles are stored in the composition without significant aggregation." But "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements

was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. “Failure to consider the claimed invention as a whole,” as Sarepta does here, “is an error of law.” *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984); *see also Rockwell Int’l Corp. v. United States*, 147 F.3d 1358, 1364 (Fed. Cir. 1998); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983).

1. The Petition Fails to Establish a Motivation to Arrive at an Ionic Strength Greater than 200 mM

Sarepta never explains “*how or why* the references would be combined to produce the claimed invention.” *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016). Neither Wu nor Konz disclose any connection between rAAV aggregation and ionic strength. Davies, ¶¶76-80. In fact, Sarepta does not point to any prior art connecting ionic strength with aggregation for therapeutic rAAV compositions. This failure is unsurprising. In 2003, shortly before the effective filing date, the “mechanism of vector aggregation [was] ***not well understood.***” EX1045, 2. The cited art does not contradict this lack of understanding. Thus, Wu and Konz alone, or in combination, do not provide a POSA with any reason to make rAAV compositions with an ionic strength greater than 200 mM.

a. The Petition Fails to Establish that Wu and Konz Connect Ionic Strength and rAAV Aggregation

Sarepta fails to identify where Wu or Konz connect ionic strength with the aggregation of high-concentration rAAV compositions. In fact, Sarepta fails to

identify any correlation in the prior art between ionic strength and any advantageous property, such as rAAV infectivity.

The Petition states that “Wu carried out electron microscopy analysis of the purified rAAV preparations” without finding evidence of aggregation. Petition, 22 (citing EX1007, 3, Fig. 3; EX1005, ¶181). The Petition further states that Wu’s “purified rAAV stock could be stored at 4°C for more than 1 month without significant decrease of infectious titer.” *Id.* (citing EX1007, 4; EX1005, ¶183.) But Wu never connects the alleged lack of aggregation and infectious titer results with ionic strength. Davies, ¶¶82-86, 115-118.

The Petition cites Wu’s disclosure relating to viral particle resuspensions in PBS²⁺ buffer to argue that a POSA would understand Wu’s compositions to meet the pH and ionic strength elements. *Id.*, 34-35 (citing EX1007, 2). Wu, however, is silent on the factors that may contribute to minimizing aggregation and maintaining infectious titer. Wu does not even disclose basic information about the pH, ionic strength, or composition of the resuspended solutions identified in the Petition. Davies, ¶¶81, 84-87 (citing EX1007). Wu’s disclosure, therefore, is insufficient to permit a POSA to assume, as Sarepta argues, that Wu’s solution is pH 7.5 to 8 or has an ionic strength above 200 mM. *Infra* §IV.A.1.c.i.

In view of the unknown characteristics regarding Wu’s formulations, a POSA would not have assumed that Wu’s electron microscopy and infectivity

results were attributable to ionic strength, and not some other factor, such as the residual chloroform or presence of PEG8000 in Wu's composition. EX1007, 4.

Neither the Petition nor Kay Declaration explain why a POSA would have had any reason to suspect, much less conclude, that ionic strength was responsible for Wu's results.

Moreover, Wu's electron microscopy analysis would not have motivated a POSA seeking to minimize aggregation to follow Wu's disclosure. A POSA would not have considered Wu's electron microscopy results to indicate the absence of aggregates in Wu's composition. Davies, ¶¶54-61. Wu focuses its electron microscopy image on a very small sample of the total number of rAAV particles to achieve the goal of analyzing the contents of monomeric particles. Wu did not assess aggregation. A POSA would have understood that Wu either avoided, or did not detect any aggregates, not because no aggregates were present, but because Wu did not analyze the composition to detect aggregation. Indeed, Wu is silent on aggregation. Wu also chemically and physically modified its rAAV sample before taking electron microscopy images. Thus, the imaging conditions were not representative of the composition's conditions, and therefore not informative of whether Wu's rAAV particles would aggregate in the composition. Davies, ¶¶115-118; *Infra* §IV.A.1.c.ii.

Konz similarly provides no connection between ionic strength and aggregation in high-concentration viral vector particle compositions. The Petition states that “Konz also discloses methods to inhibit particle aggregation and promote stability during storage, including by reference to Evans.” Petition, 36. Sarepta, however, ignores that Konz’s “sterile filtration and DLS” studies were conducted on adenovirus compositions having viral particle concentrations magnitudes below the claimed 1×10^{13} vg/ml threshold. *Id.* at 36-37 (citing EX1008, 30:13-30 (The purified adenovirus product “will be diluted to *ca.* 1.1×10^{12} vp/mL”)); 42:4-19 (“The product peak was diluted and adjusted to an adenovirus concentration of approximately 1.05×10^{12} vp/mL”), 48:4-5 (disclosing adenovirus concentrations ranging from 1.83×10^{10} vp/ml to 3.55×10^{12} vp/ml)); Davies, ¶¶77-78

Konz’s adenoviral particle concentration would also have been understood to include empty and partially filled capsids, in addition to particles with complete viral genomes. A concentration in vp/ml could have as much as a ***10-fold excess in empty capsids***, which would mean that Konz’s most concentrated adenoviral compositions of $\sim 10^{12}$ vp/ml could have a viral genome concentration of only $\sim 10^{11}$ vg/ml, 100-fold lower than the claimed rAAV concentration of 1×10^{13} vg/ml. Davies, ¶¶77-78, 119-120.

A POSA would have also understood that rAAV particle aggregation was especially a problem at high rAAV concentrations (e.g., $>10^{13}$ vg/ml). Thus, a POSA would not have considered Konz relevant to overcoming the challenge of rAAV aggregation at high concentrations. Moreover, even at lower adenoviral concentrations Konz does not address how ionic strength impacts viral particle aggregation. Davies, ¶¶77-78, 119-120. Finally, because Konz’s “formulation buffers” had ionic strengths far below 200 mM, Konz did not give a POSA any reason to increase ionic strength in rAAV compositions. *Infra* §IV.A.1.b.i.

b. Konz/Evans Would Not Motivate a POSA to Make an rAAV Composition with an Ionic Strength Greater than 200 mM

For the ionic strength element, the Petition relies on Konz’s incorporation of Evans by reference. Petition, 35-36. To reach the claimed ionic strength of greater than 200 mM, Sarepta argues that a POSA would have made a composition with the maximum recited amounts of sodium chloride (NaCl), 250 mM, disclosed in Evans. *Id.*, 36 (citing EX1005, ¶314). The Board, however, has already found that Evans would not have motivated a POSA to make the claimed rAAV compositions with an ionic strength greater than 200 mM. *Supra* §III.A. By relying on Konz’s incorporation of Evans, Sarepta’s argument is even weaker. Konz did not select Evans’ highest NaCl concentration buffer. Instead, Konz’s formulation buffers contain only 10 mM to 75 mM NaCl. Konz confirms that a POSA would also

select a much lower salt concentration buffer from Evans than Sarepta alleges, just as Konz did.

i. Sarepta Disregards that Konz's Formulation Buffers All Have Ionic Strengths Far Below 200 mM

Sarepta ignores that Konz discloses several formulation buffers, all of which contain a fraction of NaCl compared to the maximum 250 mM NaCl concentration in Evans. Right after Konz references Evans (WO 0166137), Konz discloses a list of what it refers to as “formulation buffer[s].”

The particular diafiltration buffer chosen should be an appropriate formulation buffer (see WO 0166137) or a subset of the desired components. Examples include, but are not limited to (1) 5 mM Tris, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 8.0, (2) 10 mM Tris, 10 mM Histidine, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 7.4, (3) 5 mM Tris, 10 mM NaCl, 1 mM MgCl₂, 5% sucrose, 0.005% PS-80, pH 7.4, and (4) 10 mM Tris, 10 mM Histidine, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.02% PS-80, 0.1 mM EDTA, 0.5%(v/v) ethanol, pH 7.4.

EX1008, 25:20-27. Each of Konz's formulation buffers listed above contain only 75 mM NaCl. The ionic strength contribution of the 75 mM NaCl in Konz's formulation buffers would be only 75 mM. Davies, ¶100.

Konz discloses several other formulation buffers, none of which have an NaCl concentration exceeding 75 mM.

The AEX product will be diluted to $ca. 1.1 \times 10^{12}$ vp/mL (approximately 16 liters) and is then diafiltered using flux control against 5 volumes of formulation buffer (5 mM Tris, 1 mM $MgCl_2$, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 8.0).

EX1008, 30:16-19.

The batch was diafiltered into formulation buffer (5 mM Tris, **75 mM NaCl**, 1 mM $MgCl_2$, 5% sucrose, 0.005% PS-80, pH 8.0).

Id., 42:14-15.

The batch was diafiltered into buffer (5 mM Tris, **10 mM NaCl**, 1 mM $MgCl_2$, 5% sucrose, 0.005% PS-80, pH 7.4).

Id., 52:31-32.

Konz, therefore, specifically exemplifies formulation buffers having NaCl concentrations ranging from 10 mM to 75 mM, which contribute only 10 mM to 75 mM ionic strength to Konz's enumerated formulations. The other formulation buffer components do not increase this ionic strength significantly. Davies, ¶¶97-103.

ii. Sarepta Disregards the Totality of Evans' Buffer Disclosure

Because Konz directs a POSA to buffers having ionic strengths far below the claimed 200 mM, Sarepta's ionic strength argument relies on Konz's incorporation by reference of Evans. Petition, 35-36. The Petition cites Evans' disclosure of buffers that would yield a range of NaCl concentrations from 25 mM

to 250 mM, but relies specifically on the endpoint concentration of 250 mM NaCl for the ionic strength element. Petition, 35-36 (citing EX1020; EX1005, ¶1313). But the “disclosure of a range ... does not constitute a specific disclosure of the endpoints of that range.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006). For a range to render a value obvious, a parameter must first be recognized as a “result-effective variable.” *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Sarepta fails to establish that Evans’ disclosure would render ionic strength a result-effective variable.

First, Evans itself does not contain any disclosure regarding particle aggregation. Davies, ¶104. Although the Petition alleges that Konz uses Evans’ buffer systems in particle aggregation studies, Konz’s evaluated formulation buffers all have ionic strengths far below 200 mM. *Supra* § IV.A.1.b.i. Indeed, the fact that Konz incorporates Evans by reference but exemplifies only formulation buffers with a maximum of 75 mM NaCl—notwithstanding Evans’ disclosure of an endpoint concentration of 250 mM NaCl—is strong evidence that a POSA would not have focused on Evans’ endpoint concentration as advantageous to the development of high-concentration rAAV compositions. Davies, ¶104.

Second, the Petition omits that Evans conducted stability testing only on formulations having viral particle concentrations ranging from 10^7 to 10^{11} vp/ml, which are orders of magnitude below the claimed 1×10^{13} vg/ml concentration.

EX1020, 24:21-22 and 25:13-14 (Example 2), 25:31-32 and 26:3-4 (Example 3), 29:6 (Example 7), 30:14 (Example 9); Davies, ¶104. An rAAV composition concentration expressed in vg/ml can be as much as 100-fold lower than its concentration expressed in vp/ml. *Supra* §IV.A.1.a. A POSA would have understood that aggregation was a more significant issue for high rAAV concentration compositions (e.g., $>10^{13}$ vg/ml). A POSA would not have considered Konz or Evans relevant to overcoming this challenge. *Id.*

Sarepta's argument that a POSA would have been motivated to select the upper end of the concentration ranges for NaCl in Evans' buffer system is also contradicted by Evans' stability study examples. Because all the examples in Evans were made with NaCl concentrations of 75 mM or 150 mM NaCl, none would have led a POSA to NaCl concentrations above 200 mM. Petition, 36. Other ionic species in Evans' compositions, for example $MgCl_2$ and Tris, are at such low concentrations that they do not contribute significantly to the total ionic strength of these compositions. Davies, ¶105.

In addition, Evans' tested formulations with higher concentrations of NaCl exhibited **less** stability and infectivity. Evans' exemplary formulations A105 and A104 differ only by their NaCl concentrations (150 mM NaCl in A104, 75 mM NaCl in A105) and the presence of 5% sucrose in A105 versus no sucrose in A104, as shown in the Table below. Davies, ¶106.

Example	Description
A104	5mM Tris, 150 mM NaCl , 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A105	5 mM Tris, 75 mM NaCl , 5% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0

EX1020, 22:1-2. Yet, these small differences in formulation resulted in vast differences in stability (Evans, FIG. 2) and infectivity (Evans, FIG. 3). EX1020, 24:18-25:24 (Example 2); Davies, ¶107. Figure 2 shows that the formulation with the higher NaCl concentration, A104, lost a significant amount of material after a single freeze-thaw cycle, whereas A105, with a lower NaCl concentration, lost much less.

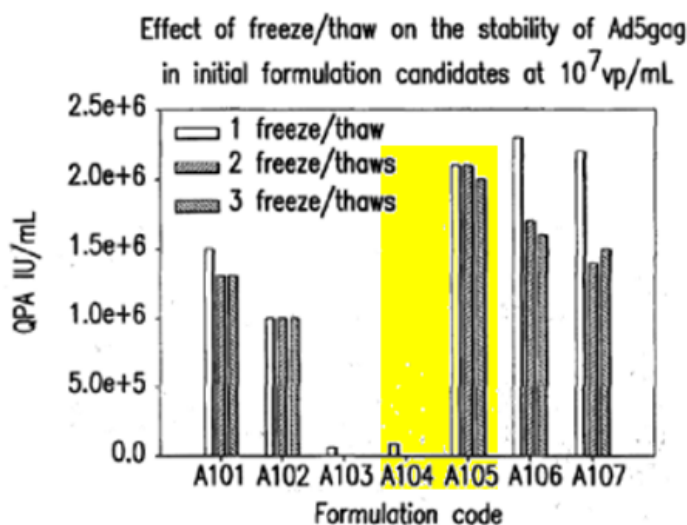


FIG.2

Figure 3 demonstrates that A105 also maintained much better infectivity than A104 after one freeze/thaw cycle. Thus, Evans' Example 2 indicates that a

lower NaCl concentration was better for ensuring viral particle stability. Davies, ¶108.

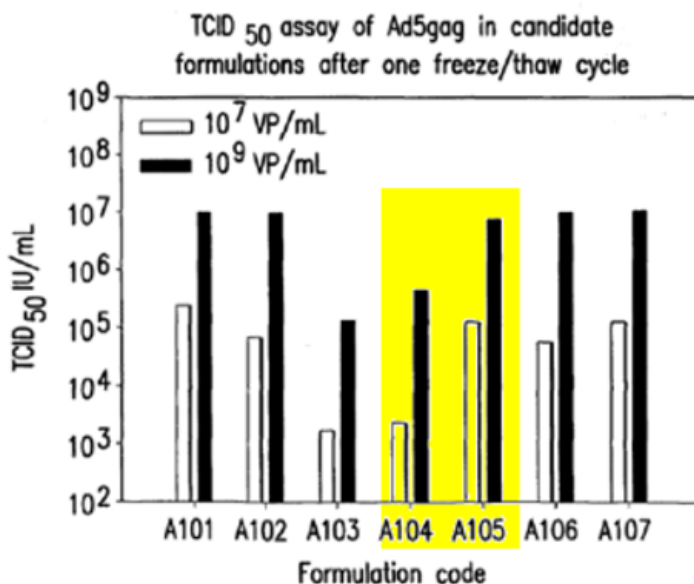


FIG.3

In the short-term stability study of Example 3, Evans compares the stability of Ad5gag in A102, A105, A106, and A107, at 10⁷ and 10⁹ vp/mL. *Id.*, 25:27-26:17. Shown below, A102 has the highest NaCl concentration (150 mM) of the tested formulations, whereas A105 has a lower NaCl concentration (75 mM), and A106 and A107 do not contain NaCl. Davies, ¶109.

Example	Description
A102	6mM phosphate, 150 mM NaCl , 10% glycerol (v/v), pH 7.2
A105	5 mM Tris, 75 mM NaCl , 5% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A106	5 mM Tris, 14% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A107	5 mM Tris, 8% sorbitol (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0

Figure 6 of Evans shows that of these formulations, A102, with the **highest NaCl concentration, lost significantly more infectivity** in 72 hours than A105, A106, and A107, as shown below with A102's results highlighted. *Id.* 26:3-17; Davies, ¶110.

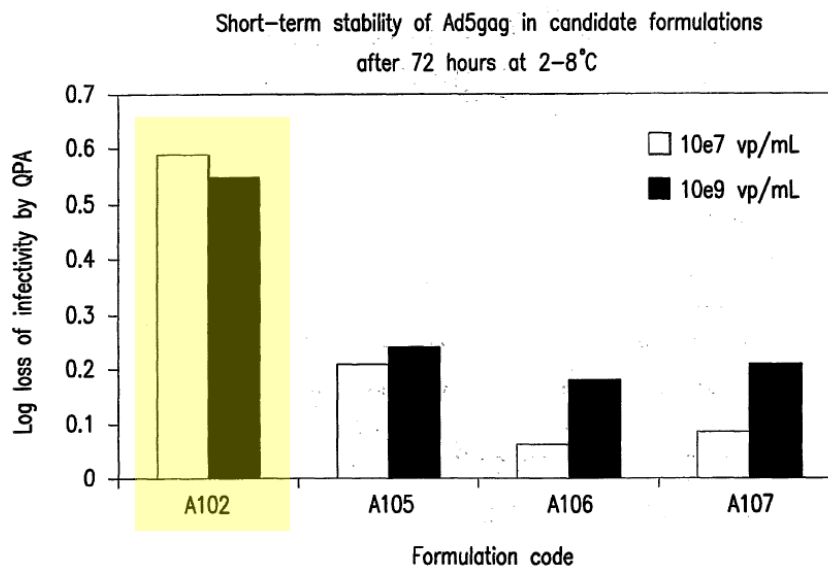


FIG.6

Evans' Example 10, which measured accelerated and real-time stability, also showed that formulations with higher NaCl concentrations, A102-A104 (each containing 150 mM NaCl), were less stable than A105, which contained a lower concentration of NaCl (75 mM NaCl). *Id.*, 30:17-25; Davies, ¶111. For an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as a POSA has “knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.” *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The Petition’s arguments disregarded Evans’ disclosure that refutes Sarepta’s theory

that a POSA would have been motivated to use Evans' high salt concentration buffer. Davies, ¶¶112-114.

iii. Konz and Evans Both Direct a POSA to Ionic Strengths Lower than 200 mM

Sarepta violates a cardinal rule of obviousness law by failing to consider the relied-upon references in their entirety. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965); *see also Henny Penny*, 938 F.3d at 1332; *W.L. Gore*, 721 F.2d at 1551. Sarepta highlights Evans' 250 mM NaCl concentration endpoint, while ignoring that Evans' stability example and Konz's formulation buffers have ionic strengths well below 200 mM. Though Sarepta focused on Evans' 250 mM NaCl concentration range endpoint, its actual reference, Konz, focused on NaCl concentrations ranging from only 10 mM to 75 mM. This alone is evidence that a POSA would not have sought to make a composition with above 200 mM NaCl. Further, Evans' data showed that viral particle stability was improved for lower ionic strength compositions containing 75 mM NaCl as compared to higher ionic strength composition containing 150 mM NaCl. This data would have led a POSA to avoid a high ionic strength buffer.

Indeed, the Board previously found substantially the same evidence not compelling in the prior IPR challenges of the '542 patent. *Supra* §III.A. The Board explained that “data presented in Evans does not establish any clear relationship between ionic strength and maintained infectivity after storage” such that a POSA would have reason to adjust ionic strength. EX1017, 23 (citing EX1016, 22-27). None of Sarepta’s evidence or argument should disturb this finding.

c. Wu Would Not Have Motivated a POSA to Make the Claimed High Ionic Strength Compositions

i. The Kay Declaration’s Calculations of Wu’s Ionic Strength Are Not Supported by Evidence

The Petition and Kay Declaration fail to establish that Wu overcomes the deficiencies of Konz/Evans. Wu does not expressly disclose an ionic strength above 200mM for any of its rAAV compositions. Sarepta, however, contends that the buffer Wu discloses to re-suspend its rAAV pellets would have resulted in an rAAV composition having an ionic strength of 209 mM or 212 mM. Petition, 35; EX1005, ¶¶299-312. The Kay Declaration admits, however, that Wu’s PBS²⁺ buffer⁴ has an ionic strength of only 169.48 mM or 172.56 mM. Therefore, the Kay Declaration supposes that residual NaCl (of at least 40 mM) from a PEG/NaCl

⁴ The Kay Declaration alleges that PBS²⁺ buffer contains a mixture of components, including Na₂HPO₄, NaCl, KCl, and KH₂PO₄. EX1005, ¶301.

precipitation employed by Wu would be present and contribute to the ionic strength. EX1005, ¶297. When summed, these values just exceed the claimed 200 mM ionic strength threshold. Wu itself, however, is silent on both the ionic strength of its PBS²⁺ buffer and the amount of residual NaCl, if any, in its precipitated pellets.

To reach its alleged ionic strength values, the Kay Declaration makes several unsupported assumptions and then conducts a series of calculations based on those fictional inputs. The inputs the Kay Declaration uses for its calculations appear to be supposition designed to reach the intended result. The inputs are not supported by the cited evidence, and the Board should give them no weight.

For the 40 mM ionic strength contribution from residual NaCl, the Kay Declaration assumes that “a POSA would have understood that there will be residual NaCl in the pellet that will be present when the pellet is resuspended in PBS²⁺ buffer.” EX1005, ¶¶175, 309. The Kay Declaration posits that “if only 0.20 ml of 1M NaCl were left in the tube when PBS²⁺ buffer was added to a final volume of 5 mls, then the concentration of NaCl in the final solution would be about 40 mM NaCl (1M NaCl diluted 0.2/5 or 1/25).” *Id.*, ¶¶176, 312.

This is pure speculation. Wu does not state anything about residual NaCl in its pellet. Nor is there any basis to assume that residual NaCl—if it existed at all—would be at a 40 mM concentration. Given the lack of disclosure, a POSA would

have not speculated regarding the amount of residual NaCl. Davies, ¶¶88-91. If, for example, there were only 20 mM of residual NaCl, leading to a 20 mM ionic strength contribution, then the ionic strengths of the resulting compositions would fall below 200 mM. EX1005, ¶312; Davies, ¶90.

Similarly, to determine the ionic strength contributed by the PBS²⁺ buffer, the Kay Declaration's calculation requires a pH value input. Wu, however, did not provide a pH value for its resuspended solutions. To determine the ionic strength contributed by the PBS²⁺ buffer, the Kay Declaration assumes that Wu's 5 mL resuspension solution is at pH 7.5-8.0. *Id.*, ¶¶287, 297, 303 n.16, 304, 309. This pH assumption is, however, speculative. Davies, ¶¶92-96.

The references that the Kay Declaration cites for the pH value indicate that PBS²⁺ buffer is typically used at pH values below this range. EX1057 ("Adjust the pH to 7.4 (or 7.2, if required)"); EX1023, 2 ("After the supernatant had run through, the column was washed with 20 ml of phosphate-buffered saline (PBS, pH 7.2)."); EX1065, 308 ("Dulbecco's phosphate-buffered saline (PBS) with Ca²⁺ and Mg²⁺, pH 7.2"); EX1083, 7 ("Prepackaged PBS (pH 7.4)"); Davies, ¶¶93-95.

According to Dr. Kay's own calculations, the lower the pH of a PBS²⁺ buffered solution, the lower its ionic strength. EX1005, ¶312 (showing a pH 7.5 PBS²⁺ solution has a lower ionic strength than a pH 8.0 PBS²⁺ solution). If Wu's solutions were at pH 7.2, for example, the ionic strength contribution of the PBS²⁺

buffer would be lower than the alleged 169.48 mM and 172.56 mM ionic strength values at pH 7.5 and pH 8.0 (*id.*). Davies, ¶96.

Sarepta provides no basis to conclude that a POSA would have understood Wu's resuspension solution to contain any NaCl, much less 40 mM. Nor does Sarepta provide any basis to assume that Wu's resuspension solution would be at pH 7.5-8.0, as required by the claims. The "[l]ack of factual support for [] expert opinion to factual determinations" renders the Kay Declaration's "testimony of little probative value in a validity determination." *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000). The Petition's reliance on the Kay Declaration's speculation as to how Wu ***could*** meet the ionic strength element, when Wu lacks the disclosure needed to determine its ionic strength, also violates Rule 104(b)(4), requiring that the petition to "specify where each element of the claim is found in the prior art patents or printed publications relied upon."⁵ Because the Kay Declaration's testimony relating to the ionic strength of Wu's

⁵ The Acting Director has reemphasized enforcement of Rule 104(b)(3), stating "applicant admitted prior art (AAPA), ***expert testimony***, common sense, and other evidence that is not 'prior art consisting of patents or printed publications' ... may not be used to supply a missing claim limitation." Memorandum on Enforcement and Non-Waiver of 37 CFR § 42.104(b)(4) (July 31, 2025) (emphasis added).

solutions is not rooted in evidence, its opinions are “entitled to little or no weight.”

37 CFR § 42.65(a).

**ii. A POSA Would Not Have Considered Wu’s
Electron Microscopy Analysis to Detect rAAV
Aggregation**

Sarepta argues that Wu’s electron microscopy studies show that its “rAAV stock formulation did not exhibit any observable aggregation.” Petition, 3; *see also id.*, 22 (citing EX1007, 3, Fig. 3). Wu, however, did not use electron microscopy to detect aggregates. Wu used electron microscopy to “visualize rAAV-GFP particles” and qualitatively observe the presence of full and intermediate rAAV particles and empty capsids. EX1007, 3. This required manipulating the sample and performing electron microscopy under conditions that were unsuitable for assessing rAAV aggregation.

Wu’s silence on aggregation confirms that its authors were not attempting to use electron microscopy to detect rAAV aggregates. Instead, Wu used electron microscopy to assess the effectiveness of its rAAV purification method. To do this, Wu focused on a small and highly magnified sample of a small number of particles, as shown below:

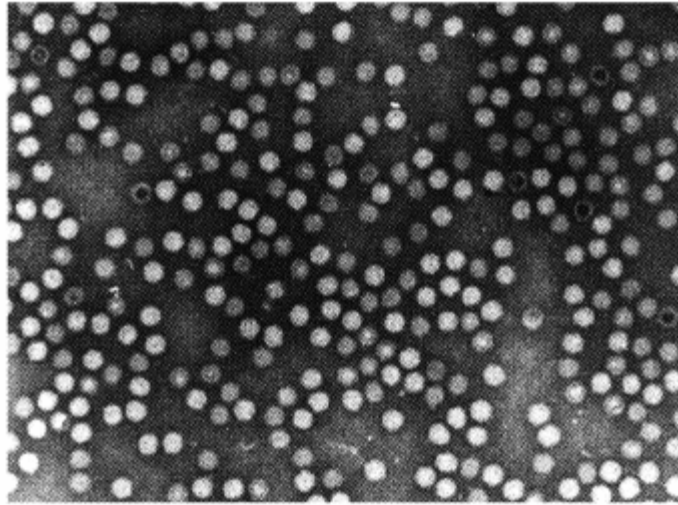


Fig. 3. Purified and concentrated recombinant adeno-associated virus particles visualized by electron microscopy after negative staining with uranyl acetate ($\times 35620$).

Id. By focusing on a small sample of monomeric particles, Wu's electron microscopy analysis was designed to detect full and intermediate rAAV particles and empty capsids, not aggregates. Wu's study was not probative of aggregation. Davies, ¶115, 117-118.

In addition, performing electron microscopy to visualize rAAV particles required manipulation of the sample. Wu extracted an aliquot of the stock, "negative staining" that sample "with 2% uranyl acetate" to visualize the individual particles, and "loading on 150 mesh nickel grids." *Id.*, 2-3. The staining and mounting of the sample significantly alters the composition's chemical environment from the stock composition. Davies, ¶116. The conditions under which electron microscopy was conducted were not representative of the composition from which the sample was drawn. Thus, they were not useful for

determining whether Wu's rAAV composition underwent significant aggregation.

Davies, ¶118.

Even if a POSA were to know the conditions of Wu's stock compositions, Wu's electron microscopy studies were not useful for detecting whether there was aggregation within the stock composition. Thus, a POSA would not have been motivated to use Wu's composition (whatever its components) in an rAAV composition that minimizes aggregation.

d. The Prior Art Directed a POSA Away from Therapeutic Compositions with High NaCl Concentrations

The Petition and Kay Declaration fail to address the many reasons why a POSA would have been motivated **not** to use a high-concentration of NaCl to achieve a high ionic strength. Prior art evidence, not considered by the Petition, indicated that high salt concentrations were undesirable for therapeutic rAAV compositions, and were even observed to negatively impact rAAV stability.

Davies, ¶121.

i. A POSA Would Have Avoided Formulations with High NaCl Concentrations that Are Hypertonic and Cause Tissue Damage and Pain When Injected

"Recognizing the difficulty of casting one's mind back to the state of technology at the time the invention was made, courts have long recognized the usefulness of evidence of the contemporaneous attitude toward the asserted invention." *Interconnect Plan. Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

As of the effective filing date, a major concern that would have driven the development of therapeutic rAAV formulations was isotonicity. Davies, ¶122. The prior art “emphasize[d] the two formulation parameters, pH and tonicity, that are usually associated with tissue damage and injection pain and “provides a parenteral product development outline” that includes guidance on ways in which pH and tonicity “may be modified to minimize tissue damage and pain caused by a parenteral product.” EX2019, 3-4; *see also* EX2017, 4 (“Solutions to be administered subcutaneously **require strict attention to tonicity** adjustment.”).

POSA would have understood that to minimize tissue damage and pain, the osmolarity of therapeutic rAAV formulations should be close to serum osmolarity. Serum osmolarity is about 300 mOsm. EX2016, 57. “Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% [~150 mM] sodium chloride solution, are referred to commonly, as being hypotonic. Physiological solutions having a greater osmotic pressure are termed hypertonic.” *Id.*, 55; *see also* EX1001, 5:15-16. A 300 mOsm NaCl solution is isosmotic with 300 mOsm serum, and thus isotonic. Davies, ¶123. Thus, a POSA would have understood that “optimal formulations for pre-clinical and clinical studies **should be close to isotonic** (280-400 mOsm), especially for *in vivo* administration of vector to sites where dilution of hypertonic solutions may be slow.” EX1001, 5:4-7. “For an

isotonic product, often it is ***advantageous to keep the concentration of salt as low as possible.***” EX2018, 197.

Sarepta’s obviousness argument relies on a POSA selecting the Evans buffer containing 250 mM NaCl and 5 mM MgCl₂. This buffer would have an osmolarity of 515 mOsm (500 mOsm from NaCl and 15 mOsm from MgCl₂), which is much higher than 300 mOsm serum, and is therefore hypertonic. Davies, ¶124. A POSA, who would be concerned about the adverse effects of hypertonicity, including pain and tissue damage, would not have been motivated to use a buffer formulation with an osmolarity of 515 mOsm. *Id.*, ¶125.

The Petition’s motivation argument focuses on modifying Wu, which contains toxic chloroform, to make it suitable for therapeutic use by exchanging Wu’s buffer with a buffer from Konz/Evans. Sarepta argues that “a POSA would have been motivated to remove residual chloroform from Wu’s rAAV stocks by exchanging Wu’s buffer with a buffer in Konz (as incorporated via Evans).” Petition, 32; *see also id.*, 3; EX1007, 4 (“Further steps should be taken to remove residual chloroform before the stocks are used in clinical trials.”).

Evans taught that its virus formulations should be made “useful for parenteral, and especially intramuscular, injection.” EX1020, 10:18-21. The state of the art emphasized that injectable formulations should be isotonic, particularly

for “intramuscular delivery,” which is Evans’ “especially preferred method” of delivery. *Id.*, 20:17-18; Davies, ¶127.

Sarepta fails to prove obviousness by not explaining why a POSA focused on making formulations suitable for clinical use nonetheless would have been motivated to substitute Wu’s buffer with a hypertonic buffer inappropriate for such use. *See Trivascular*, 812 F.3d at 1068 (finding no motivation to modify the prior art where doing so “would destroy the basic objective” of the prior art); *see also Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022) (holding “the board did not adequately grapple with why a skilled artisan would find it obvious” to modify the prior art in a manner that would undermine a critical property of that art.). Neither Sarepta nor Dr. Kay explain why a POSA would have violated the principle of maintaining isotonicity, when a POSA would have considered such an issue central to formulation development. Davies, ¶¶126-128.

Despite the evidence showing that isotonicity was an important consideration in developing therapeutic compositions, Sarepta argues for making a composition having an NaCl concentration of 250 mM, which greatly exceeds this isotonic threshold. Petition, 35-36. This contradiction exposes that Sarepta’s case for obviousness “is only straightforward in hindsight.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013).

ii. High Salt Concentrations Were Observed to Promote Precipitation of rAAV Particles

High salt concentration solutions were also observed to cause instability of rAAV particles. Davies, ¶¶129-130. For example, Xie (EX1028) explained that “[h]igh concentrations of AAV-2 in the ~3.3 M CsCl from ultracentrifugal purification remained mostly in solution at 4°C, although there was some precipitation and adhesion to glass- and plastic-ware with time....” EX1028, 7. Thus, even for *molar* salt solutions of CsCl having osmolarity of ~ 6600 mOsm that would be unsuitable as parenteral formulations, AAV particle precipitation was observed. Moreover, Xie further stated that a solution of “0.25 M NaCl [250 mM] resulted in **significant loss**” of AAV. *Id.* Thus, Xie teaches that a salt concentration of 250 mM NaCl, the NaCl concentration that Sarepta advocates (Petition, 35-36), was observed as inadequate to prevent significant rAAV aggregation in Xie’s solution. Xie’s observation, published near the time of the effective filing date, contradicts the Petition’s motivation argument. Davies, ¶129.

Xie, however, was not the only reference to suggest that high salt concentrations could lead to undesirable results for rAAV compositions. For example, WO 99/41416, published Aug. 19, 1999, to Frei et al. (EX2020), which was relied-upon prior art in IPR2023-00608, states that a POSA “must take into account the additional **threat to stability posed by the high salt concentrations.**” EX2020, 19:9-14; *see also id.*, 18:19-24; 21:25-26; 21:42-22:6. Sarepta also

disregards this reference. Davies, ¶130. In an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as a POSA has “knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.” *Dow*, 837 F.2d at 473. Fairly considering the evidence disregarded in its Petition, Sarepta has failed to establish a motivation to make the claimed composition having an ionic strength greater than 200 mM. Davies, ¶131.

e. The Petition Improperly Incorporates Arguments About a POSA’s Alleged Background Knowledge by Reference

The Petition alleges that Sarepta “relies on background, state of the art references (that were also not before the Patent Office during prosecution or the PTAB during the prior IPR proceedings) to demonstrate that a POSA at the relevant date would have been well aware that ionic strength was a ‘results-effective variable’ for viral particle aggregation.” Petition, 19 (citing EX1030; EX1031; EX1032); *see also id.*, 11 (citing EX1005, ¶¶36-88). Despite these lofty statements, however, the only explanation the Petition provides is that the “Floyd studies showed that dilution of viral particle preparations, which reduces ionic strength, can result in aggregation.” *Id.*, 11 (citing EX1030, Abstract, 2; EX1005, ¶¶38-39). The Petition never ties these brief mentions of background art to the motivation argument. To the extent Sarepta’s submissions address this background

art, the Petition improperly incorporates all arguments from the Kay Declaration, as explained in Genzyme’s discretionary denial submissions. *See* Paper 8.

“Arguments must not be incorporated by reference from one document into another document.” 37 C.F.R. § 42.6(a)(3); *see also* PTAB Consolidated Trial Practice Guide, 35-36 (Nov. 2019) (“CTPG”). “The burden of production cannot be met simply by throwing mountains of evidence at the Board without explanation or identification of the relevant portions of that evidence.” *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1371 (Fed. Cir. 2023). The Board is not required “to play archeologist with the record....” *3M Co. v. Evergreen Adhesives, Inc.*, 860 F. App’x 724, 725 (Fed. Cir. 2021) (internal quotations omitted); *see also* CTPG at 35-36; *Parus*, 70 F.4th at 1372 (holding that “the prohibition against incorporation of arguments . . . eliminate[s] abuses that arise from incorporation and combination.”) (internal quotations omitted); *Nearmap US, Inc. v. Pictometry Int’l Corp.*, IPR2024-00729, Paper 9 at 21-22 (PTAB Oct. 10, 2024).

The Petition imports by reference four publications and 53 paragraphs of the Kay Declaration. Petition, 11 (citing EX1030; EX1031; EX1032; EX1041, 6; EX1005, ¶¶36-88.). Sarepta’s incorporation of arguments by reference circumvents the word count requirement and allows for multiple grounds for every claim. *Id.*, 9. Sarepta burdened Genzyme with sifting through Sarepta’s lengthy submissions,

including the 182-page Kay Declaration and responding to those arguments in its own word-limited Preliminary Response. To maintain a fair process, the Board should not consider this testimony improperly incorporated by reference. CTPG at 35-36.

f. A POSA Would Not Have Considered Sarepta's Cited Background Art Relevant to rAAV Compositions

The “background, state of the art references” or “Floyd studies” (EX1030-EX1032) relate to 1970s era research on disinfecting virus-containing “water passing through sewage or water treatment plants.” EX1030, 1. A POSA looking to prepare rAAV compositions for therapeutic use in 2004 would not have considered such references relevant to rAAV aggregation. Davies, ¶132.

Floyd's study of the disinfection of poliovirus and reoviruses for water treatment is relevant to disinfecting sewage streams with agents such as chlorine or bromine. EX1030, 1. Aggregation allowed viruses to evade disinfectants, whereas disrupting viral aggregates allowed disinfecting agents to access and inactivate the viruses. *Id.*, 1, 8; Davies, ¶133.

In contrast, a POSA formulating an rAAV composition, who would be seeking to maximize infectivity, would not consider the Floyd studies, which focused on eliminating infectivity. The demands of developing a therapeutic composition that will be injected into a human are completely different than treating sewage and water supplies. Davies, ¶¶133-134.

A POSA also would not have considered the poliovirus and reovirus subjects of the Floyd study to exhibit behavior as representative of rAAV particles. Davies, ¶135. For example, “[i]n the pH region of 7 to 10.5, both poliovirus and reovirus showed *no tendency to aggregate*.” EX1032, 6 (emphasis added). In contrast, researchers observed aggregation of rAAV particles at pH 8.0. EX1001, 1:65-2:8; EX1045, 3; EX2022, 3-4.

Additionally, the Floyd references studied viral aggregation on “[p]article concentrations of stocks [that] ranged from 10^{10} to 2×10^{12} particles/ml.” EX1030, 1; EX1005, ¶39. A POSA understood that rAAV aggregation is concentration dependent. EX2021, 6; EX1045, 2; Davies, ¶135. The Kay Declaration acknowledges that aggregation led to significant losses in infectivity in high-concentration rAAV compositions above 10^{13} vg/ml, such that high-concentration compositions could be less infective than lower concentration compositions. EX1005, ¶36 (citing EX1043). Therefore, the Floyd studies, which dealt with much lower viral concentrations, would not have been relevant to a POSA developing high concentration rAAV compositions. Davies, ¶¶135-136.

2. Sarepta’s Ground 1 Fails to Establish a Reasonable Expectation that a High Ionic Strength rAAV Composition Could be Stored Without Significant Aggregation

As a “touchstone of obviousness,” a reasonable expectation of success requires not only an “expectation that prior art elements are capable of being

physically combined, but also that the combination would have ***worked for its intended purpose.***” *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). Sarepta fails to establish that the prior art would have led a POSA to a reasonable expectation that the claimed compositions having an ionic strength greater than 200 mM could have been stored without significant aggregation. The inventors were the first to overcome rAAV aggregation at “concentration[s] exceeding 1×10^{13} vg/ml” by formulating compositions with an ionic strength of greater than 200 mM that did not exhibit significant aggregation. *Supra* §II.A (citing EX1001, Figs. 1A, 1B). This was neither predictable nor expected given the state of the art at the time of invention. Davies, ¶¶137-141.

a. Sarepta Fails to Consider the Unpredictability of Liquid Biological Formulations

Carpenter states that “[i]t can be assumed that ***most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed.***” EX2018, 198. Carpenter further explains that “[e]very protein and product has unique characteristics, some of which may cause difficulty in designing stable formulations.” *Id.*, 130; Davies, ¶141. Considering references that Sarepta cites, including Huang, Croyle, and Wright (2003), a POSA would have been skeptical that high-concentration rAAV aqueous compositions would have been feasible. *Supra* §IV.A.1.d; Davies, ¶¶142-145. Evans demonstrated that even for a single viral vector, minor changes in excipients can produce dramatic changes

in stability. *Supra* §IV.A.1.b.ii (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3) (comparing stabilities of formulations A104 and A105).

The Board should find here, as it has before (*supra* §III.A), that a reasonable expectation of success argument that fails to account for and rebut this well-recognized unpredictability cannot prove obviousness. *Amneal Pharms. LLC v. Cubist Pharms. LLC*, IPR2020-00193, Paper 7 at 22-32 (PTAB May 29, 2020); *Sandoz Inc. v. AbbVie Biotechnology Ltd.*, IPR2017-01823, Paper 16 at 14 (PTAB Feb. 9, 2018); *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-01018, Paper 14 at 4 (PTAB Feb. 2, 2017); *Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Paper 37 at 12-13 (PTAB Dec. 22, 2016).

b. The Combination of Konz/Evans and Wu Fails to Establish a Reasonable Expectation of Success

Sarepta ignores that Konz's "sterile filtration and DLS" studies were conducted on adenovirus compositions having concentrations magnitudes below the claimed 1×10^{13} vg/ml threshold. Petition, 36-37 (citing EX1008, 30:13-30 (The purified adenovirus product "will be diluted to *ca.* 1.1×10^{12} vp/mL"); 42:4-19 ("The product peak was diluted and adjusted to an adenovirus concentration of approximately 1.05×10^{12} vp/mL"), 48:4-5 (disclosing adenovirus concentrations ranging from 1.83×10^{10} vp/ml to 3.55×10^{12} vp/ml)). A POSA would not have considered these results to be predictive of aggregation of higher concentration

rAAV compositions, which were known to present more significant aggregation issues. *Supra* §IV.A.1.a; Davies, ¶¶146-147.

Similarly, Evans, which is cited by Konz and relied on by Sarepta for the ionic strength element (Petition, 35-36), conducted stability testing only on formulations having viral particle concentrations ranging from 10^7 vp/mL to 10^{11} vp/ml, which is several orders of magnitude below both the 10^{13} vp/ml upper limit of Evans' concentration range and the 1×10^{13} vg/ml threshold of the claims. EX1020, 24:21-22 and 25:13-14 (Example 2), 25:31-32 and 26:3-4 (Example 3), 29:6 (Example 7)); Davies, ¶¶148-149.

Additionally, none of the exemplary formulations in Konz or Evans have a NaCl concentration greater than 150 mM NaCl. *Supra* §§IV.A.1.a, IV.A.1.b.ii. Konz does not address rAAV aggregation and discloses several formulation buffers, none of which have an NaCl concentration exceeding 75 mM. In Evans, the most stable formulations contained 75 mM or less NaCl, with ionic strengths below 200 mM. Evans nonetheless demonstrated that even small changes to excipients can dramatically change the stability of a viral vector composition, with the highest NaCl concentration buffer resulting in the poorest stability results. *Id.* (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3); Davies, ¶150.

Wu does not even disclose basic information about the pH, ionic strength, or composition of its resuspended solutions; the Petition relies on speculative

assumptions made in the Kay Declaration. *Supra* §IV.A.1.c.i. Because of this lack of information, a POSA would not have been able to discern what components of Wu's formulation may contribute to Wu's storage data. Petition, 22 (citing EX1007, 4; EX1005, ¶183). Further, a POSA would not have considered Wu's electron microscopy analyses as accurately measuring the extent of aggregation in Wu's stock solution. *Supra* §IV.A.1.c.ii. Therefore, Wu lacks any disclosure regarding both ionic strength and aggregation that a POSA would need to determine whether elevated ionic strength decreased aggregation. Davies, ¶151.

Thus, Sarepta fails to point to any disclosure in Wu, Konz, or Evans that would have supplied a POSA with a reasonable expectation that compositions comprising rAAV particles at concentrations $>10^{13}$ vg/ml and an ionic strength greater than 200 mM would not result in significant aggregation. Davies, ¶152. Sarepta has failed to meet its burden.

B. Ground 2: The Petition's Combination of Wu, Konz, and Croyle Fails to Render Claim 3 Obvious

Claim 3 requires the same combination of elements that the Petition fails to prove obvious in Ground 1. The Petition cites Croyle (EX1009) solely to address the Pluronic F68 claim requirements in claim 2 and 3. Petition, 45-49. The addition of Croyle does not overcome the deficiencies of Sarepta's proofs for the other elements of claim 3. Thus, Sarepta's Ground 2 fails for claim 3 for the same reasons Ground 1 fails. *Supra* §IV.A; Davies, ¶¶153-154.

C. Ground 3: The Petition’s Combination of Potter and Konz Fails to Render Claims 3-6 Obvious

The Petition fails to establish how substituting Potter for Wu merits a different result than Ground 1. *Davies*, ¶156. Sarepta repeats its strategy of assembling disparate disclosures from Potter and Konz/Evans for the rAAV concentration, ionic strength, and no significant aggregation elements without explaining why it would have been obvious for a POSA to make a composition with the claimed combination of elements. *KSR*, 550 U.S. at 418. Once again, Sarepta’s “[f]ailure to consider the claimed invention as a whole,” as Sarepta does here, “is an error of law.” *Jones*, 727 F.2d at 1529; *see also Rockwell*, 147 F.3d at 1364; *W.L. Gore.*, 721 F.2d at 1548.

1. The Petition Fails to Establish a Motivation to Arrive at an Ionic Strength Greater than 200 mM

As explained in Ground 1 (*supra* §IV.A.1), the “mechanism of vector aggregation [was] **not well understood**” for rAAV compositions. EX1045, 2. Like Wu, Potter never addresses rAAV aggregation, much less any factors that influence rAAV aggregation. Sarepta never explains “*how or why* the references would be combined to produce the claimed invention.” *TriVascular*, 812 F.3d at 1066. Potter and Konz alone, or in combination, do not provide a POSA with any reason to make rAAV compositions with an ionic strength greater than 200 mM for multiple reasons. *Davies*, ¶¶157-158.

**a. The Petition Fails to Establish that Potter and Konz
Connect Ionic Strength and rAAV Aggregation**

The Petition states that “Potter discloses an electron microscopy analysis of the purified rAAV particles ... There is no evidence of aggregation in this study.” Petition, 54 (citing EX1010, 16-17, Fig. 5; EX1005, ¶419). But Potter never addresses rAAV aggregation in its purified rAAV particles or connects the alleged lack of aggregation with the ionic strength of the storage composition. Sarepta alleges that Potter’s stock compositions are stored in a buffer containing a 0.5 M NaCl, which would have an ionic strength of 500 mM. *Id.*, 53 (citing EX1010, 7). But the compositions that Sarepta cites for ionic strength are in a separate embodiment from the composition Sarepta cites for the high rAAV concentration. *Id.*, 51 (citing EX1010, 19 [*sic*], Table II). And the composition that Sarepta cites for the no significant aggregation element is yet another separate composition that has undergone further chemical manipulation. *Id.*, 54 (citing EX1010, 16-17, Fig. 5). Sarepta fails to provide any reason for why a POSA would combine these separate rAAV composition embodiments into a single embodiment satisfying the rAAV concentration, ionic strength, and no significant aggregation claim elements. Davies, ¶¶156-157. Thus, neither the Petition nor Kay Declaration explain why a POSA would have had any reason to suspect, much less conclude, that ionic strength was responsible for Potter’s results.

As explained for Ground 1, Sarepta fails to identify where Konz/Evans connects ionic strength with any advantageous property (such as lack of aggregation or rAAV infectivity). *Supra* §IV.A.1.a. Sarepta, likewise, fails to identify where Potter connects ionic strength with rAAV aggregation (or any advantageous property), because Potter does not do so. The POSA would not have been motivated to follow Potter's disclosure in order to prevent significant aggregation of rAAV particles. Davies, ¶157. Like Wu, Potter's electron microscopy analysis focused on analyzing a small, highly magnified, sample of a purified composition. And, like Wu, Potter manipulates the chemical and physical environment of the rAAV particles for its analysis so that they are no longer representative of the aggregation of particles contained in the composition for storage. *Id.*, ¶¶172-182.

b. Konz/Evans Would Not Motivate a POSA to Make an rAAV Composition with an Ionic Strength Greater than 200 mM

For the ionic strength element, the Petition relies on Konz's incorporation of Evans by reference. Petition, 54-55 (citing EX1005, ¶¶420-422). Sarepta makes the same arguments for Ground 3 as in Ground 1, and thus the Petition fails to establish motivation for the same reasons as described for Ground 1. *Supra* §IV.A.1.b. Sarepta ignores that Konz discloses several formulation buffers, all of which contain a fraction of NaCl (10-75 mM) compared to the maximum 250 mM

NaCl concentration in Evans. *Supra* §IV.A.1.b.i. Sarepta's arguments disregard the totality of Evans' teachings that would have directed a POSA to lower salt concentration, and, therefore, lower ionic strength rAAV compositions for multiple reasons. *Supra* §IV.A.1.b.ii. In sum, Konz and Evans, considered in their totality, directed a POSA to rAAV compositions having ionic strength values much lower than 200 mM. *Supra* §IV.A.1.b.iii; Davies, ¶¶159-161.

c. Potter Would Not Motivate a POSA to Make the Claimed rAAV Compositions with an Ionic Strength Greater than 200 mM

Sarepta's argument fails to establish that a POSA would have considered Potter to disclose the claimed rAAV compositions with an ionic strength greater than 200 mM. The Petition cites to Potter's "National Reference Standard rAAV." Petition, 51-52; EX1005, ¶¶397-403 (citing EX1010, Table II). Potter, however, does not provide specifics as to ionic strength or even to the components of the National Reference Standard rAAV composition. Without this information, a POSA would be unable to determine ionic strength. Davies, ¶162.

For ionic strength information, the Petition and Kay Declaration cite to a different composition in Potter, an rAAV composition resulting from the elution of a heparin affinity chromatography purification step that contains 0.5 M (500 mM) NaCl. Petition, 53; EX1005, ¶¶413-414; EX1010, 7. The Petition and Kay Declaration, however, never explain why a POSA would have understood the

National Reference Standard rAAV composition to have the same buffer system as the chromatographic purification elution composition. Davies, ¶163-171. A POSA would have considered the compositions summarized in Table I to be different than the compositions in Table II.

i. Potter's rAAV Large-Scale Production Compositions

Potter discloses a protocol for purifying rAAV comprising three chromatographic steps. For its ionic strength proof, Sarepta cites the solution used to elute the viral particles, “PBS containing 0.5 M NaCl.” Petition, 52-53 (citing EX1010, 7; EX1005, ¶413). Potter summarizes the results of this purification in Table I, shown below.

[24]

rAAV LARGE-SCALE PRODUCTION

419

TABLE I
SUMMARY OF rAAV-UF5 PURIFICATION

Run	Crude lysate		Streamline heparin affinity chromatography		HIC phenyl sepharose chromatography		Heparin affinity chromatography	
	Total inf. particles	% yield	Total inf. particles	% yield	Total inf. particles	% yield	Total inf. particles	% yield
1	4.8×10^{12}	100	2.7×10^{12}	56	2.3×10^{12}	48	1.3×10^{12}	27
2	9.6×10^{12}	100	1.8×10^{13}	186	1×10^{13}	104	4.2×10^{12}	43
3	3.6×10^{12}	100	1.2×10^{12}	33	1.3×10^{12}	36	1.2×10^{12}	33

EX1010, 7.

The rAAV product yields are provided in “total inf[ectious] particles,” but Potter does not disclose the rAAV concentration in the eluted rAAV solution. Potter states that the final step results in several “[one] ml fractions ... collected”

of the eluted rAAV solution, but it does not state how many total fractions of the purified product are collected. EX1010, 4-7. It is not possible to determine the concentration of rAAV particles in each 1 ml fraction without knowing the total volume of the collected solutions. For example, if ten one milliliter fractions were pooled to result in the highest yielding run of 4.2×10^{12} infectious particles, each fraction would have a concentration of only 4.3×10^{11} infectious particles/ml, roughly **100X less** than the claimed concentration of 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml. Davies, ¶¶163-166. Even if only one ml fraction were collected, a concentration of $1.2\text{-}4.2 \times 10^{12}$ infectious particles per ml is about **10X less** than the claimed concentration. A POSA would have understood, however, that multiple one milliliter fractions were likely pooled. Davies, ¶165. Therefore, the concentrations for each run would have likely been even lower than 10^{13} vg/ml, respectively, for runs 1-3. Davies, ¶166.

ii. Potter's National Reference Standard rAAV Compositions

A POSA would have understood that the concentrations in Potter's National Reference Standard composition are considerably higher than the pooled fractions from Table 1. Davies, ¶166. Potter is silent on how it arrives at its National Reference Standard rAAV composition or what components are present in that composition. A POSA would not assume that the National Reference Standard rAAV composition had the same buffer system as the large scale production batch

pooled fractions. Davies, ¶¶168-170. Sarepta never explains how a POSA would infer from Potter that the eluted rAAV composition was the same as the National Reference Standard rAAV. Sarepta “has the responsibility to make plain its challenges to the disputed claims.” *Nearmap*, IPR2024-00729, Paper 9 at 20-21 (citing 37 C.F.R. § 42.104(b)(4)); *see also id.* (citing 37 C.F.R. § 42.22(a)(2)) (“It is not the Board’s responsibility to weave together Petitioner’s evidence into a cohesive case.”); *Parus*, 70 F.4th at 1371-72. Sarepta does not satisfy its responsibility.

Sarepta also fails to supply any reason for why it would have been obvious to use Potter’s large scale purification buffer system with its National Reference Standard rAAV composition. “It is not sufficient to demonstrate that each of the components in a challenged claim is known in the prior art; Petitioner must also explain why a POSITA would have combined the elements disclosed in the separate embodiments described” in a single reference. *Intel Corp. v. Tela Innovations, Inc.*, IPR2019-01521, Paper 65 at 25 (PTAB Mar. 9, 2021) (citing *KSR*, 550 U.S. at 418); *see also In re Stepan Co.*, 868 F.3d 1342, 1345–46 n.1 (Fed. Cir. 2017) (If obviousness is based on “combining multiple embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.”).

iii. Sarepta Misrepresents Prior Genzyme Submissions Regarding the Potter Reference

Genzyme's Preliminary Response in IPR2023-00608, responding to arguments made by Novartis (EX1014, 13, 15), correctly explained that Potter's rAAV compositions on page 419 (EX1010, 7), which had a buffer containing PBS²⁺ and 0.5 M NaCl and "reported yields of $1.2\text{-}4.2 \times 10^{12}$ total infectious particles," had rAAV concentrations "well below the claimed rAAV concentration." EX1016, 48. As explained above (*supra* §IV.C.1.c.i.), Dr. Davies previously explained that the experiments that Potter discloses on page 419 "relate to pooled fractions from column chromatography experiments, so the 10^{12} total infectious particles are likely in several milliliters of solution." EX1060, ¶123. "Thus, the viral genome concentrations in Potter's cited experiments are likely significantly below 10^{13} vg/ml." *Id.*; Davies, ¶167.

Sarepta, however, accuses Genzyme and Dr. Davies of materially "mischaracteriz[ing] the concentration of the disclosed formulations in Potter," Petition, 15-16, based on the rAAV concentration of Potter's National Reference Standard rAAV composition on page 421. EX1010, 9. Neither Genzyme nor Dr. Davies, however, addressed Potter's National Reference Standard rAAV composition, Petition, 16 (citing EX1010, 9-10), because Potter provides no information about the ionic strength of this composition. Likewise, the petition in IPR2023-00608, which cited Potter's 0.5 M NaCl buffer on pages 417-419 of

Potter, did not cite the National Reference Standard rAAV composition on page 421 of Potter. EX1014, 13, 15 (citing EX1010, 5-7).

This is not surprising. There is nothing in the record to support Sarepta's contention that the elution buffer for the chromatographic purification on page 419 is also present in the National Reference Standard rAAV composition on page 421. Davies, ¶170. Dr. Kay's supporting testimony for the rAAV concentration and ionic strength elements never explains why a POSA would assume the elution buffer is present in Potter's National Reference Standard rAAV composition. EX1005, ¶¶397-402, 413-414; Davies, ¶171. Thus, the Kay Declaration's opinion for these issues is "conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight." *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential) (citing 37 C.F.R. § 42.65(a)).

iv. A POSA Would Not Have Considered Potter's Electron Microscopy Analysis to Accurately Detect rAAV Aggregation

Sarepta also alleges that Genzyme "incorrectly characterized the analytical method, electron microscopy" as not being useful to detect aggregates. Petition, 16. But as explained for Wu, a POSA would not have considered Potter's electron microscopy analysis focused on characterizing monomeric particles as useful for detecting aggregates in an rAAV composition. *Supra* §IV.A.1.c.ii. The Petition

alleges that “Potter discloses electron microscopy studies showing that the rAAV stock formulation did not exhibit any observable aggregation.” Petition, 6; *see also id.*, 17, 54 (citing EX1010, 16-17, Fig. 5). Potter, however, did not use electron microscopy to detect aggregates. Potter used electron microscopy to “confirm the structure of infectious and noninfectious particles.” EX1010, 17; Davies, ¶¶172-176. A POSA, therefore, would have understood Potter’s use of electron micrographs to detect full, partial, and empty rAAV particles, but not aggregation. *Id.*, 16-17, Fig. 5. To confirm particle structure, Potter magnified a small sample of particles that was not representative of the composition from which they were isolated. Davies, ¶176. Thus, the sample size and degree of magnification was not useful for detecting the presence or absence of aggregates. *Id.*

As with Wu, to visualize rAAV particles, Potter also conducted several steps that drastically changed the surrounding environment of those particles. **First**, “[t]o confirm the structure of infectious and noninfectious particles [by electron microscopy], two peaks from the continuous iodixanol gradient are concentrated by POROS HPLC chromatography.” EX1010, 17. Iodixanol is an iodine-containing non-ionic radiocontrast agent. Potter explains that a “continuous gradient of iodixanol ... is formed by mixing virus with 30% iodixanol prepared in PBS containing 0.9 M MgCl₂. The sample is transferred into a quick-sealing tube, placed in a Ti-70 rotor, and spun at 70,000 rpm for 8 hr at 15°. After

centrifugation, the sample is fractionated by puncturing the tube at the bottom and collecting 1 ml fractions.” *Id.*, 14. Then that sample further undergoes POROS chromatography. *Id.*, 17. **Second**, “[f]ollowing chromatography, [electron microscopy] analysis of concentrated samples is performed ... by placing 5 µl of purified virus stock on support films of Formvar/Carbon 400 mesh copper grids ... for 1 min.” *Id.* **Third**, the sample is then “stained with 5 µl of 2% uranyl acetate for 10 sec[onds].” *Id.*

The separation, isolation, staining, and mounting of the sample significantly altered the composition’s chemical environment from the stock composition. Davies, ¶¶177-181. The conditions under which electron microscopy was conducted was not representative of the solution from which the sample was drawn, and therefore not useful for determining whether Potter’s rAAV composition underwent significant aggregation. Davies, ¶182. Neither the Petition nor Kay Declaration addresses this issue.

Accordingly, even if a POSA were to know the conditions of Potter’s stock compositions, Potter’s electron microscopy studies would not have been considered useful for detecting whether there was aggregation in that stock composition. Thus, a POSA would not have been motivated to use Potter’s composition (whatever its components) in rAAV compositions that minimize aggregation.

d. The Prior Art Directed a POSA Away from Therapeutic Compositions with High NaCl Concentrations

As with Ground 1, Ground 3 fails to address the many reasons why a POSA would have been motivated *not* to make high NaCl concentration rAAV compositions. *Supra* §IV.A.1.d. Sarepta's failure to address these issues is even more glaring because the rAAV composition that the Petition points to has 500 mM of NaCl, which is double the uppermost value of Evans at 250 mM.

i. A POSA Would Have Understood that Potter's Compositions Comprising 500 mM NaCl Concentrations Are Hypertonic and Likely to Cause Tissue Damage and Pain

As explained for Ground 1, a POSA would have understood that therapeutic compositions should be close to isotonic (280-400 mOsm). *Supra* §IV.A.1.d.i. The high salt buffer disclosed in Evans that Sarepta relies on for the ionic strength element is hypertonic, with an osmolarity of 515 mOsm. *Id.* The 500 mM NaCl buffer that Sarepta points to in Ground 3 (Petition, 53), would have an osmolarity of 1000 mOsm accounting for the added NaCl alone, rendering it extremely hypertonic. Davies, ¶183-185.

Sarepta fails to prove obviousness by not explaining why a POSA focused on making formulations suitable for clinical use nonetheless would have been motivated to make a formulation having a salt concentration that high, resulting in a hypertonic solution. *See Chemours*, 4 F.4th at 1376. Neither Sarepta nor Dr. Kay

explain why a POSA would have violated the principle of maintaining isotonicity when a POSA would have considered such an issue central to formulation development.

Sarepta reaches the claimed multivalent ion and ionic strength claim elements only using hindsight. Despite the evidence showing that isotonicity was an important consideration in developing therapeutic compositions, Sarepta argues for making a composition having an NaCl concentration of 250 mM, which greatly exceeds this isotonic threshold. Petition, 35-36. This contradiction exposes that Sarepta's case for obviousness "is only straightforward in hindsight." *Leo*, 726 F.3d at 1355.

ii. High Salt Concentrations Were Observed to Promote Precipitation of rAAV Particles

Solutions with high salt concentrations were also observed to cause instability of rAAV particles. *Supra* §IV.A.1.d.ii; Davies, ¶¶186-187. As explained, Xie disclosed that an AAV composition containing of "0.25 M NaCl [250 mM] resulted in **significant loss**" of AAV. EX1028, 23. Thus, a POSA would not have been motivated to use Evans' 250 mM NaCl solution out of concern for rAAV stability. *Contra* Petition, 53-54. A POSA would have been less motivated to use Potter's 500 mM NaCl buffer (*id.*, 53), which has twice the NaCl concentration of Evans. Davies, ¶¶186-187.

2. Sarepta's Ground 3 Fails to Establish a Reasonable Expectation that a High Ionic Strength rAAV Composition Could be Stored Without Significant Aggregation

For the same reasons explained for Ground 1, Sarepta fails to establish a reasonable expectation, based on Potter and Konz, that the claimed compositions having an ionic strength greater than 200 mM could have been stored without significant aggregation. *Supra* §IV.A.2. The POSA would have found it unpredictable to develop high-concentration rAAV compositions that remain stable without significant aggregation. *Supra* §IV.A.2.a. As explained, Konz's aggregation and stability studies did not address the unique challenges of formulating **high-concentration** rAAV compositions that do not exhibit significant aggregation when stored. *Supra* §IV.A.2.b.

Sarepta fails to establish that Potter's stock solution has an ionic strength of greater than 200 mM. *Supra* §IV.C.1.c.ii. Potter does not even disclose basic information about the pH, ionic strength, or composition of stock solution; the Petition merely speculates, without supporting evidence, that the buffer system in the stock solution is the same as used for purification. Because of this lack of information, a POSA would not have been able to discern what components of Potter's formulation may contribute to its storage data. Petition, 29 (citing EX1010, 17; EX1005, ¶¶243-46); Davies, ¶¶189-191. Further, a POSA would not have considered Potter's electron microscopy analyses as accurately measuring the

extent of aggregation in Potter's stock solution. *Supra* §IV.C.1.c.iv; Davies, ¶190.

Therefore, Potter lacks any disclosure regarding both ionic strength and aggregation that a POSA would need to determine whether elevated ionic strength decreased aggregation. Davies, ¶190.

Thus, Sarepta fails to point to any disclosure in Potter, Konz, or Evans that would have supplied a POSA with a reasonable expectation that compositions comprising rAAV particles at concentrations $>10^{13}$ vg/ml and an ionic strength greater than 200 mM would not result in significant aggregation. Sarepta has failed to meet its burden.

D. Ground 4: The Petition's Combination of Potter, Konz, and Croyle Fails to Render Claim 3 Obvious

Claim 3 requires the combination of elements that the Petition fails to render obvious through Potter and Konz in Ground 3. The Petition cites Croyle (EX1009) solely to address the Pluronic F68 claim requirements in claim 2 and 3. Petition, 60-65. The addition of Croyle does not overcome the deficiencies of Sarepta's proofs for the other elements of claim 3. Thus, Sarepta's Ground 4 fails for claim 3 for the same reasons that Ground 3 fails. *Supra* §IV.C; Davies, ¶192.

V. CONCLUSION

For the foregoing reasons, the Petition should be denied, and no proceeding instituted.

Respectfully submitted,

Dated: October 8, 2025

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WORD COUNT CERTIFICATION

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Preliminary Response contains 13,988 words (excluding the title page, table of contents, table of exhibits, this certificate, and the certificate of service), as determined by Microsoft Word.

Dated: October 8, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that today in

Sarepta Therapeutics, Inc., v. Genzyme Corporation, IPR2025-01194

I caused to be served copies of:

PATENT OWNER’S PRELIMINARY RESPONSE

EXHIBITS 2015-2029, 2031-2032

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